

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125477Orig1s000

CHEMISTRY REVIEW(S)

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.0

Instructions:

The review team should email this form to the email account “CDER-TB-EER” to submit:

- 1) an initial TB-EER within 10 business days of the application filing date
- 2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing¹ locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA/BsUFA Action Date: April 23, 2014

Applicant Name: Eli Lilly and Co.

U.S. License #: 1891

STN: BLA 125477/0

Product: Cyramza (ramucirumab)

Short summary of application: Treatment of advanced gastric cancer or gastroesophageal junction adenocarcinoma, as a single agent after prior fluoropyrimidine- or platinum-containing therapy.

FACILITY INFORMATION

Firm Name: ImClone Systems LLC

Address: 33 ImClone Drive
Branchburg, NJ 08876 USA

FEI: 3002889358

Short summary of manufacturing activities performed: Drug substance manufacture, release and stability testing

This site was inspected by NWJ-DO from 11/4/2013 – 11/13/2013 and classified NAI. This was a PLI for ramucirumab and a routine CGMP surveillance inspection covering biotech drug substance manufacturing and testing operations. The CBI profile is updated and is acceptable.

¹The regulations at 21 C.F.R. § 207.3(a)(8) defines “manufacturing or processing” as “the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer.”

Firm Name: Eli Lilly and Company
Address: Indianapolis, Indiana 46285USA
FEI: 1819470

Short summary of manufacturing activities performed: Drug product manufacture, release and stability testing; secondary packaging/labeling of drug product

This site was inspected by DET-DO on April 15 – 19, 2013 and classified VAI. This was a routine CGMP surveillance inspection covering sterile drug product manufacturing operations. The CBI and (b) (4) profiles were updated and are acceptable.



This site was inspected by (b) (4) on (b) (4) and classified VAI. This was a routine CGMP surveillance inspection covering biotech drug substance testing operations. The CTL profile was updated and is acceptable.



This site was inspected by (b) (4) on (b) (4) and classified VAI. This was a routine CGMP surveillance inspection covering biotech drug testing operations. The (b) (4) profile was updated and is acceptable.



This site was inspected by (b) (4) on (b) (4) and classified NAI. This was a routine CGMP surveillance inspection covering biotech drug testing operations. The (b) (4) profile was updated and is acceptable.

This site was inspected by (b) (4) on (b) (4) and classified NAI. This was a routine CGMP surveillance inspection covering biotech drug testing operations. The CTL profile was updated and is acceptable.

OVERALL RECOMMENDATION

There are no pending or ongoing compliance actions that prevent approval of this application.

APPEARS THIS WAY ON ORIGINAL

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/s/

CHRISTINA A CAPACCI-DANIEL
04/01/2014

SUMMARY BLA125477 ramucirumab (Cyramza)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drugs Evaluation and Research – Food and Drug Administration
Office of Biotechnology Products / Office of Pharmaceutical Science
Division of Monoclonal Antibodies

The Quality Team Leader's Executive Summary

From: Sarah Kennett, Ph.D., Review Chief
Division of Monoclonal Antibodies (DMA)

Through: Kathleen A. Clouse, Ph.D., Director
DMA/OBP/OPS/CDER

BLA Number: 125477
Product: Ramucirumab (Cryamza)
Sponsor: Eli Lilly and Company

Date of Review: January 23, 2014
Date of CDTL Memo: March 26, 2014

SUMMARY BLA125477 ramucirumab (Cyramza)

I. RECOMMENDATIONS AND CONCLUSIONS ON APPROVABILITY

The Division of Monoclonal Antibodies, Office of Biotechnology Products, OPS, CDER, recommends approval of STN 125477 for ramucirumab (Cyramza) manufactured by Eli Lilly. The data submitted in this application are adequate to support the conclusion that the manufacture of ramucirumab (Cyramza) is well controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use (under conditions specified in the package insert).

II. APPROVAL LETTER INFORMATION

Under this license, you are approved to manufacture the ramucirumab drug substance at ImClone Systems LLC in Branchburg, NJ. Ramucirumab (Cyramza) drug product will be manufactured at Eli Lilly and Company in Indianapolis, IN.

The dating period for ramucirumab drug product shall be 36 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined (b) (4)

The dating period for ramucirumab drug substance shall be (b) (4) from the date of manufacture when stored a (b) (4)

III. POST MARKETING COMMITMENTS/POST MARKETING REQUIREMENTS

PMC #1 - To re-evaluate ramucirumab drug substance lot release and stability specifications after (b) (4) lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided by XXXX, XX, XXXX (date to be provided by Eli Lilly).

PMC #2 - To re-evaluate ramucirumab drug product lot release and stability specifications after (b) (4) lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided by XXXX, XX, XXXX (date to be provided by Eli Lilly).

PMC #3 - To confirm product stability (b) (4) using small scale studies. These studies will include testing (b) (4) for product quality (purity by (b) (4), and potency of ramucirumab). Final study reports will be provided by XXX, XX, XXXX (date to be provided by Eli Lilly).

SUMMARY BLA125477 ramucirumab (Cyramza)

PMC #4 - To perform a shipping study designed to confirm validation of the commercial ramucirumab drug product shipping conditions. The study will include monitoring of temperature during the shipment, testing of pre- and post-shipment samples for product quality (purity by SEC, rSDS-PAGE, nrSDS-PAGE, IEX, (b) (4) and potency of ramucirumab), and confirmation that the commercial shipping configuration minimizes physical damage to drug product containers. The final study report will be provided by XXX, XX, XXXX (date to be provided by Eli Lilly).

PMR #1 - To develop a validated, sensitive, and accurate assay for the detection of binding antibodies to ramucirumab, including procedures for accurate detection of binding antibodies to ramucirumab in the presence of ramucirumab levels that are expected to be present in the serum or plasma at the time of patient sampling. The validation report will be submitted as a Prior Approval Supplement by XXX, XX, XXXX (date to be provided by Eli Lilly).

PMR #2 - To develop a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to ramucirumab, including procedures for accurate detection of neutralizing antibodies to ramucirumab in the presence of ramucirumab levels that are expected to be present in the serum or plasma at the time of patient sampling. The validation report will be submitted as a Prior Approval Supplement by XXX, XX, XXXX (date to be provided by Eli Lilly).

IV. LIST OF DEFICIENCIES TO BE COMMUNICATED

None

V. EXECUTIVE SUMMARY

A. Description of Ramucirumab (Cyramza) drug substance and drug product

Ramucirumab is a full length recombinant, human, immunoglobulin IgG1, κ monoclonal antibody (IMC-1121B, LY3009806) that is directed to VEGFR-2 (human vascular endothelial growth factor receptor-2), a membrane protein expressed predominantly on vascular endothelial cells. Ramucirumab is comprised of two heavy chains (446 amino acid residues, (b) (4)) and two light chains (214 amino acid residues). (b) (4)

(b) (4). The total molecular weight of ramucirumab is approximately (b) (4)

146,756 Da.

Ramucirumab drug product is supplied as a sterile, preservative-free liquid solution at 10 mg/ml in (b) (4) mL and 50 mL single-dose vials. Ramucirumab drug product is formulated in 10 mM histidine (b) (4) sodium chloride, (b) (4) glycine, and (b) (4) polysorbate 80, pH 6.0. (b) (4)

SUMMARY BLA125477 ramucirumab (Cyramza)

(b) (4) As supplied, the solution of ramucirumab drug product has a clear to slightly opalescent, colorless to slightly yellow appearance that is free from visible particles. It is supplied in single-use, (b) (4) vials containing 100 mg (nominal) ramucirumab and in 50 mL vials containing 500 mg (nominal) ramucirumab for intravenous (IV) infusion. The extractable volume of each (b) (4) vial is 10 mL, and the extractable volume of each 50 mL vial is 50 mL.

The extinction coefficient was calculated to be (b) (4). The experimentally determined extinction coefficient is (b) (4). The theoretical value has been used since early development and will continue to be used to determine ramucirumab protein concentration.

The intended long term storage temperature for ramucirumab drug product is 2-8°C. The primary packaging components for ramucirumab drug product consist of a USP/Ph. Eur./JP Type 1, (b) (4) mL or 50 mL (b) (4) glass, (b) (4) vial that is sealed with a (b) (4) stopper and (b) (4) seal.

Ramucirumab is diluted into 0.9% saline to a total volume of 250 mL immediately prior to administration and administered through a protein sparing 0.22 µm filter. The diluted infusion solution can be stored at 2-8°C for up to 24 hours or at room temperature (below 25°C) for up to 4 hours.

The ramucirumab drug product vials (b) (4)

A claim for a categorical exclusion from the Environmental Assessment (EA) requirement has been submitted under 21CFR section 25.31(c), which states that any application for marketing approval of a biologic product for substances that occur naturally in the environment, or supplement to such an application, is categorically excluded and ordinarily does not require an EA or an Environmental Impact Statement when there is not a significant alteration of the concentration or distribution of the substance, its metabolites or degradation product in the environment. The sponsor states that no extraordinary circumstances exist with respect to this product. There is no indication that additional environmental information is warranted. The claim of categorical exclusion is deemed acceptable.

B. Clinical Trial Information

Ramucirumab is intended for use as a single agent for the treatment of patients with advanced gastric cancer or gastro-esophageal junction adenocarcinoma after prior chemotherapy.

SUMMARY BLA125477 ramucirumab (Cyramza)

The route of administration of ramucirumab is IV infusion. The recommended dosing is 8 mg/kg every 2 weeks until disease progression or unacceptable toxicity. Infusions are carried out over 60 minutes (b) (4).

The pivotal clinical study (REGARD; I4T-IE-JVBD; IMCL CP12-0715) was a randomized, double-blind, multi-center, international phase 3 trial of ramucirumab plus best supportive care versus placebo plus best supportive care in patients with advanced gastric cancer that had progressed after combination chemotherapy. Patients were randomized in a 2:1 ratio to ramucirumab or placebo. In the ramucirumab arm, treatment was given for a median of 4 cycles, and in the placebo arm, treatment was given for a median of 3 cycles; each cycle was 14 days.

The primary efficacy endpoint of overall survival was a median of 5.2 months in the ramucirumab arm and 3.8 months in the placebo arm. The secondary endpoint of progression free survival (PFS) was 2.1 months in the ramucirumab arm and 1.3 months in the placebo arm; the secondary endpoint of the 12 week PFS rate was 40.1% in the ramucirumab arm and 15.8% in the placebo arm.

Phase 3 clinical trials are ongoing in hepatocellular carcinoma, breast cancer lung cancer, and colorectal cancer and also in combination with paclitaxel for gastric cancer.

This BLA was granted priority review status.

C. Stability

The BLA submission contained adequate stability data to support establishment of a drug substance and drug product shelf-life. Stability studies have been conducted in accordance with ICH Q1A(R2) and Q5C. Drug substance and drug product stability protocols, including specifications, conditions and testing intervals, were provided and determined to be acceptable.

- The data support a shelf life of (b) (4) from the date of manufacture for the ramucirumab drug substance when stored at (b) (4). Although data are provided only through 18 months for four registration batches at (b) (4), there are data demonstrating stability out to (b) (4) for additional representative drug substance batches.
- Stability tests for drug substance lots stored at (b) (4) include visual appearance, color, osmolality, pH, protein concentration, potency by bioassay, potency by binding assay, (b) (4) endotoxin, and bioburden. All tests were performed at 0, 3, 6, 9, 12, 15 (3 lots only), 18, and 24 months.
- The most sensitive stability-indicating assays for drug substance were shown to be (b) (4).

SUMMARY BLA125477 ramucirumab (Cyramza)

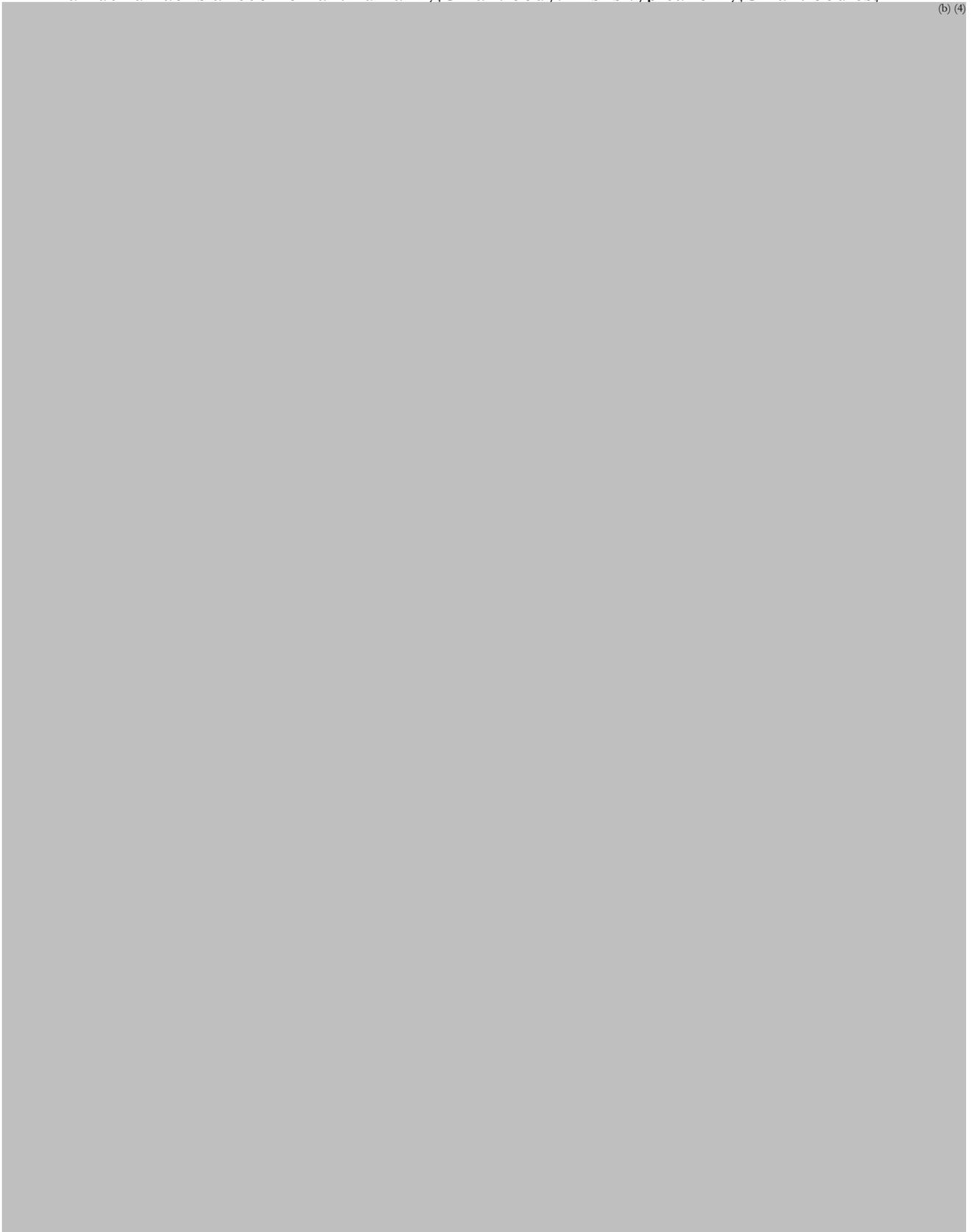
- The post-approval drug substance annual stability protocol will store samples at (b) (4) and include tests for visual appearance, color, clarity, osmolality, pH, protein concentration, potency by bioassay, potency by binding assay, (b) (4), endotoxin, and bioburden. Testing will be performed at 0, 3, 6, 9, 18, and 24 months, with the exception of bioburden and endotoxin, which will be tested annually.
- The data support a shelf life of 36 months from the date of manufacture for ramucirumab (Cyramza) drug product when stored at 2-8°C. The date of manufacture is defined (b) (4). Although data are provided only through 12 months for the registration batches at 2-8°C, there are data demonstrating stability out to 36 months for additional representative drug substance batches.
- Stability tests for drug product lots stored at 2-8°C include visual appearance, color, clarity, osmolality, pH, protein concentration, potency by bioassay, potency by binding assay, (b) (4), (b) (4), particulate matter, endotoxin, sterility, and CCI. Most tests were performed at 0, 1, 3, 6, 9, 12, 24, 30, and 36 months with 15, 18, and 21 month timepoints added for 4 lots; osmolality, pH, and protein concentration are not included at the 1, 3, 9, and 30 month time points, and endotoxin, sterility, and CCI are not included at the 1, 3, 6, 9, and 30 month time points.
- The most sensitive stability-indicating assays for drug product were shown to be (b) (4).
- The post-approval annual drug product stability protocol will store samples from each presentation at 2-8°C and include tests for visual appearance, color, clarity, osmolality, pH, protein concentration, potency by bioassay, potency by binding assay, (b) (4), (b) (4), particulate matter, sterility, and CCI. Most testing will be performed at 0, 3, 6, 9, 12, 18, 24, and 36 months; osmolality, pH, protein concentration, sterility, and CCI will be performed annually.
- Stressed studies included temperature excursion, freeze/thaw, and photostability.
- Photostability studies indicated that ramucirumab is light sensitive and should not be exposed to intense light for prolonged periods of time.
- Freeze/thaw studies performed on ramucirumab drug substance support up to (b) (4) freeze-thaw cycles, demonstrating a lack of adverse effects from temperature cycling.
- Drug product does not contain preservatives. Drug product vials are single-dose and should be discarded after use.

D. Complexity

SUMMARY BLA125477 ramucirumab (Cyramza)

Ramucirumab is a recombinant human IgG1 antibody. As is typical of IgG1 antibodies,

(b) (4)



SUMMARY BLA125477 ramucirumab (Cyramza)

F. Mechanism of Action

Ramucirumab acts through binding to VEGFR-2 and blocking the interaction of VEGFR-2 with its ligand, VEGF. Blocking of this interaction leads to inhibition of VEGFR activation and downstream signaling. (b) (4)

Ramucirumab inhibits binding of VEGF-A, VEGF-C, and VEGF-D (b) (4)

Two assays are used to measure ramucirumab potency, an (b) (4)

(b) (4)

G. Manufacturing Process

(b) (4)

(b) (4)

(b) (4) Drug product vials are stored at 2-8°C.

H. Comparability

There have been four drug substance manufacturing processes during the development of ramucirumab: Process A, used for phase 1 clinical studies; Process B, used for phase 2 and early phase 3 clinical studies; Process C0, used for the majority of the phase 3 studies; and Process C1 (commercial).

(b) (4)

SUMMARY BLA125477 ramucirumab (Cyramza)

(b) (4)

- Drug substances derived from the first three processes (A through C0) were determined to be sufficiently comparable to support the clinical trials at the respective phases.

(b) (4)

Drug product changes during development included the change in formulation associated with the drug substance Process A to Process B change.

(b) (4)

(b) (4)

- Drug products manufactured using each process were determined to be sufficiently comparable to support the clinical trials at the respective phases.
- Drug products manufactured using C0 drug substance and C1 drug substance and manufactured at (b) (4) and Lilly sites have been determined to be sufficiently comparable to support use of stability data from drug product manufactured using the C0 drug substance and stability data from drug product manufactured at (b) (4) to support the expiry period for commercial drug product. Similarly, the (b) (4) presentation and the 50 mL presentation are sufficiently comparable to allow the use of 50 mL vial stability data in support of the expiry period for the (b) (4) vial.

I. Immunogenicity

(b) (4)

SUMMARY BLA125477 ramucirumab (Cyramza)

(b) (4)



(b) (4) The concern regarding the inability of the assays to detect ADA in samples containing drug was communicated to the clinical pharmacology and clinical reviewers, and PMRs to develop assays with increased drug tolerance will be implemented.

VI. SIGNATURE BLOCK

Kathleen A. Clouse, Ph.D.
Director
Division of Monoclonal Antibodies

Sarah Kennett, Ph.D.
Review Chief
Division of Monoclonal Antibodies

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/s/

SARAH B KENNETT
01/27/2014

KATHLEEN A CLOUSE STREBEL
01/27/2014

BLA STN 125477

CyramzaTM (ramucirumab)

Eli Lilly and Company

Michele K. Dougherty, Ph.D., Reviewer
Sarah Kennett, Ph.D., Review Chief

Division of Monoclonal Antibodies

Product Quality Review Data Sheet

1. **BLA#** STN 125477

2. **REVIEW DATE:** January 22, 2014

3. **PRIMARY REVIEW TEAM:**

Medical Officer: Sandra Casak, M.D.; Steve Lemery, M.D., (Team Leader and Cross Disciplinary Team Leader)

Pharm/Tox: Sachia Khasar, Ph.D.; Whitney Helms, Ph.D., (Team Leader)

Product Quality Team: Michele K. Dougherty, Ph.D. (Primary Reviewer); Sarah Kennett, Ph.D. (Team Leader, Review Chief)

BMAB: Candace Gomez-Broughton, Ph.D., (Drug Product); Kalavati Suvarna, Ph.D., (Drug Substance); Patricia Hughes, Ph.D. (Team Leader)

Clinical Pharmacology: Lillian Zhang, Ph.D.; Hong Zhao, Ph.D. (Team Leader)

Statistics: Hui Zhang, Ph.D.; Kun He, Ph.D. (Team Leader)

OBP Labeling: Michele K. Dougherty, Ph.D. (Primary Reviewer); Sarah Kennett, Ph.D. (Team Leader, Review Chief)

RPM: Sharon Sickafuse

4. **MAJOR GRMP DEADLINES**

Filing Meeting: October 7, 2013 (GRMP date: October 22, 2013)

Mid-Cycle Meeting: December 2, 2013

Wrap-Up Meeting: March 17, 2014

Primary Review Due: January 23, 2014

Secondary Review Due: January 30, 2014

CDTL Memo Due: March 26, 2014

PDUFA Action Date: April 23, 2014

5. **COMMUNICATIONS WITH SPONSOR AND OND:**

Communication/Document	Date
CMC Pre-BLA Meeting	January 23, 2013
Teleconference 1	January 17, 2014
Information Request #1	July 22, 2013
Information Request #2	October 31, 2013
Information Request #3	December 10, 2013
Information Request #4	December 17, 2013
Information Request #5	December 31, 2013
Information Request #6	January 9, 2014
Information Request #7	January 10, 2014
Information Request #8	January 16, 2014
Information Request #9	January 21, 2014

6. SUBMISSION(S) REVIEWED:

Submission	Date Received	Review Completed (Yes/No)
STN 125477/0.1 (Immunogenicity Validation)		Yes
STN 125477/0.3 (Response to IR #1)	July 29, 2013	Yes
STN 125477 /0.5 (Quality Module)	August 23, 2013	Yes
125477/0.9 (Response to filing letter comments)	November 4, 2013	Yes
125477/0.12 (response to BMAB IR)	November 15, 2013	Yes
125477/0.13 (Response to IR # 2)	November 19, 2013	Yes
125477/0.17 (Response to IR #3)	December 13, 2013	Yes
125477/0.19 (Response to IR #4)	December 23, 2013	Yes
125477/0.21 (Response to IR #5)	January 9, 2014	Yes
125477/.22 (Response to IR #6)	January 15, 2014	Yes
125477/0.23 (Response to IR #7)	January 17, 2014	Yes
125477/0.24 (Response to IR #8)	January 20, 2014	Yes
125477/0.26 (Response to IR #9)	January 23, 2014	Yes

7. DRUG PRODUCT NAME/CODE/TYPE:

- a. Proprietary Name: CYRAMZA
- b. Trade Name: Cyramza
- c. Non-Proprietary/USAN: ramucirumab
- d. CAS name: 947687-13-0
- e. Common name: IgG1 κ , anti-human vascular endothelial growth factor receptor-2 (VEGF-2) extracellular domain
- f. INN Name: ramucirumab
- g. Compendial Name: N/A
- h. OBP systematic name: MAB HUMAN (IGG2) ANTI P35968 (VGFR2_HUMAN) [LY3009806]
- i. Other Names: IMC-1121B; LY3009806

8. PHARMACOLOGIC CATEGORY: Therapeutic monoclonal antibody to the human vascular endothelial growth factor 2 receptor (VEGFR2)

9. DOSAGE FORM: concentrate for solution

10. STRENGTH/POTENCY:

- a) The concentration of Cyramza Drug Product is 10 mg/ml in 10 ml and 50 ml presentations.
- b) Potency is determined by two assays. (b) (4)

(b) (4)

- c) The dating period for vial drug product is 36 months when stored at 2-8°C.
- d) 100 mg of ramucirumab is filled into (b) (4) glass vials; 500 mg of ramucirumab is filled into 50 ml glass vials.

11. ROUTE OF ADMINISTRATION: Intravenous

12. REFERENCED MASTER FILES:

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
(b) (4)			Yes	No review required as all the relevant information related to compatibility with the product was in the BLA.
			Yes	No review required as all the relevant information related to compatibility with the product was in the BLA
			Yes	No review required as all the relevant information related to compatibility with the product was in the BLA
			Yes	No review required as all the relevant information related to compatibility with the product was in the BLA

(b) (4)	Yes	No review required as all the relevant information related to compatibility with the product was in the BLA
	Yes	No review required as all the relevant information related to compatibility with the product was in the BLA

13. INSPECTIONAL ACTIVITIES

The pre-license inspection of the drug substance manufacturing site at ImClone Systems, LLC, Branchburg NJ was conducted on November 4-8, 2013 and November 13, 2013 by Michele K. Dougherty, DMA, and Alberto Vicedo, New Jersey District Office. The inspection covered the manufacturing of drug substance in the BB-50 manufacturing areas. The inspection was system-based and covered Quality, Production, Laboratory Control, Materials, Packaging and Labeling, and Facilities and Equipment Systems. No Form FDA483 was issued. It was recommended that the inspection be classified as no action indicated. The pre-license inspection of the drug product manufacturing site was waived.

14. CONSULTS REQUESTED BY OBP

None Requested

15. QUALITY BY DESIGN ELEMENTS

The following QbD elements were submitted (check all that apply):

	Design Space
x	Design of Experiments
x	Formal Risk Assessment / Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

Risk assessments to identify critical quality attributes of ramucirumab and to identify process parameters for assessment in process characterization studies were performed according to methods described in the submission and review of Module 3.

A design of experiments (DoE) approach was utilized to generate process understanding. Results from DoE experiments were used to support the overall control strategy proposed for ramucirumab drug substance. The sponsor does not claim a design space.

16. PRECEDENTS

None

17. ADMINISTRATIVE

Kathleen A. Clouse, Ph.D.
Director, Division of Monoclonal Antibodies

Sarah Kennett, Ph.D.
Review Chief, Division of Monoclonal Antibodies

Michele K. Dougherty, Ph.D.
Primary Reviewer
Division of Monoclonal Antibodies

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/s/

MICHELE K DOUGHERTY
01/23/2014

SARAH B KENNETT
01/23/2014

KATHLEEN A CLOUSE STREBEL
01/23/2014

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

BLA/NDA Number: 125477 **Applicant:** Eli Lilly and Company **Stamp Date:** August 23, 2013
Established/Proper Name: Ramucirumab **BLA/NDA Type:** BLA

On **initial** overview of the BLA/NDA application for filing:

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y	
Form 356h completed	Y	
<input type="checkbox"/> including list of all establishment sites and their registration numbers	Y	
Comprehensive Table of Contents	Y	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y	
Labeling:	Y	
<input type="checkbox"/> PI –non-annotated	Y	
<input type="checkbox"/> PI –annotated	Y	
<input type="checkbox"/> PI (electronic)	N/A	
<input type="checkbox"/> Medication Guide	N/A	
<input type="checkbox"/> Patient Insert	N/A	
<input type="checkbox"/> package and container	Y	
<input type="checkbox"/> diluent	N/A	
<input type="checkbox"/> other components	N/A	
<input type="checkbox"/> established name (e.g. USAN)	Y	
<input type="checkbox"/> proprietary name (for review)	Y	

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	Y	
<input type="checkbox"/> legible	Y	
<input type="checkbox"/> English (or translated into English)	Y	
<input type="checkbox"/> compatible file formats	Y	
<input type="checkbox"/> navigable hyper-links	Y	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	Y	
<input type="checkbox"/> summary reports reference the location of individual data and records	Y	
<input type="checkbox"/> all electronic submission components usable (e.g. conforms to published guidance)	Y	
Companion application received if a shared or divided manufacturing arrangement	N/A	

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y	
Introduction to the summary documents (1 page) [2.2]	Y	
Quality overall summary [2.3]	Y	
<input type="checkbox"/> Drug Substance	Y	
<input type="checkbox"/> Drug Product	Y	
<input type="checkbox"/> Facilities and Equipment	Y	
<input type="checkbox"/> Adventitious Agents Safety Evaluation	Y	
<input type="checkbox"/> Novel Excipients	N/A	
<input type="checkbox"/> Executed Batch Records	Y	
<input type="checkbox"/> Method Validation Package	Y	
<input type="checkbox"/> Comparability Protocols	Y	

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	Y	
Drug Substance [3.2.S]		
<input type="checkbox"/> general info	Y	
<input type="checkbox"/> nomenclature		
<input type="checkbox"/> structure (e.g. sequence, glycosylation sites)		
<input type="checkbox"/> properties		
<input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)	Y	
<input type="checkbox"/> description of manufacturing process and process control	Y	
<input type="checkbox"/> batch numbering and pooling scheme		
<input type="checkbox"/> cell culture and harvest		
<input type="checkbox"/> purification		
<input type="checkbox"/> filling, storage and shipping		
<input type="checkbox"/> control of materials	Y	
<input type="checkbox"/> raw materials and reagents		
<input type="checkbox"/> biological source and starting materials		
<input type="checkbox"/> cell substrate: source, history, and generation		
<input type="checkbox"/> cell banking system, characterization, and testing		
<input type="checkbox"/> control of critical steps and intermediates	Y	
<input type="checkbox"/> justification of specifications		
<input type="checkbox"/> stability		

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present?	If not, justification, action & status
<input type="checkbox"/> process validation (prospective plan, results, analysis, and conclusions) <input type="checkbox"/> manufacturing process development (describe changes during non-clinical and clinical development; justification for changes) <input type="checkbox"/> characterization of drug substance <input type="checkbox"/> control of drug substance <ul style="list-style-type: none"> ○ specifications ○ justification of specs. ○ analytical procedures ○ analytical method validation ○ batch analyses <input type="checkbox"/> reference standards <input type="checkbox"/> container closure system <input type="checkbox"/> stability <ul style="list-style-type: none"> □ summary □ post-approval protocol and commitment □ pre-approval <ul style="list-style-type: none"> ○ protocol ○ results ○ method validation 	 Y Y Y Y Y Y Y Y Y	
Drug Product [3.2.P] [Dosage Form] <input type="checkbox"/> description and composition <input type="checkbox"/> pharmaceutical development <ul style="list-style-type: none"> ○ preservative effectiveness ○ container-closure integrity <input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved) <input type="checkbox"/> batch formula <input type="checkbox"/> description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities) <input type="checkbox"/> controls of critical steps and intermediates <input type="checkbox"/> process validation including aseptic processing & sterility assurance: <ul style="list-style-type: none"> ○ Filter validation ○ Component, container, closure depyrogenation 	 Y Y N/A Y Y Y Y Y Y	

**PRODUCT QUALITY (Biotechnology)
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CTD Module 3 Contents	Present?	If not, justification, action & status
<ul style="list-style-type: none"> and sterilization validation <ul style="list-style-type: none"> ○ Validation of aseptic processing (media simulations) ○ Environmental Monitoring Program ○ Lyophilizer validation ○ Other needed validation data (hold times) <input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin) <input type="checkbox"/> control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities) <input type="checkbox"/> reference standards or materials <input type="checkbox"/> container closure system [3.2.P.7] <ul style="list-style-type: none"> ○ specifications (vial, elastomer, drawings) ○ availability of DMF & LOAs ○ administration device(s) <input type="checkbox"/> stability <ul style="list-style-type: none"> <input type="checkbox"/> summary <input type="checkbox"/> post-approval protocol and commitment <input type="checkbox"/> pre-approval <ul style="list-style-type: none"> ○ protocol ○ results ○ method validation 	<p>N/A</p> <p>Y</p> <p>Y</p> <p>Y</p> <p>Y</p> <p>N/A</p> <p>Y</p>	
<p>Diluent (vials or filled syringes) [3.2P']</p> <ul style="list-style-type: none"> <input type="checkbox"/> description and composition of diluent <input type="checkbox"/> pharmaceutical development <ul style="list-style-type: none"> ○ preservative effectiveness ○ container-closure integrity <input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved) <input type="checkbox"/> batch formula <input type="checkbox"/> description of manufacturing process for production through 		<p align="right">(b) (4)</p> <p>the diluent section is not applicable</p>

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CTD Module 3 Contents	Present?	If not, justification, action & status
<p>finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)</p> <ul style="list-style-type: none"> <input type="checkbox"/> controls of critical steps and intermediates <input type="checkbox"/> process validation including aseptic processing & sterility assurance: <ul style="list-style-type: none"> <input type="checkbox"/> Filter validation <input type="checkbox"/> Component, container, closure depyrogenation and sterilization validation <input type="checkbox"/> Validation of aseptic processing (media simulations) <input type="checkbox"/> Environmental Monitoring Program <input type="checkbox"/> Lyophilizer sterilization validation <input type="checkbox"/> Other needed validation data (hold times) <input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients) <input type="checkbox"/> control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities) <input type="checkbox"/> reference standards <input type="checkbox"/> container closure system <ul style="list-style-type: none"> <input type="checkbox"/> specifications (vial, elastomer, drawings) <input type="checkbox"/> availability of DMF & LOAs <input type="checkbox"/> stability <ul style="list-style-type: none"> <input type="checkbox"/> summary <input type="checkbox"/> post-approval protocol and commitment <input type="checkbox"/> pre-approval <ul style="list-style-type: none"> <input type="checkbox"/> protocol <input type="checkbox"/> results 		
<p>Other components to be marketed (full description and supporting data, as listed above):</p> <ul style="list-style-type: none"> <input type="checkbox"/> other devices <input type="checkbox"/> other marketed chemicals (e.g. part 	<p>N/A N/A</p>	

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Examples of Filing Issues	Yes?	If not, justification, action & status
trial to commercial production lots		
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y	
Certification that all facilities are ready for inspection	Y	
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y	
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: <input type="checkbox"/> LAL instead of rabbit pyrogen <input type="checkbox"/> mycoplasma <input type="checkbox"/> sterility	Y Y N/A N/A	
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y	
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y	
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y	

**PRODUCT QUALITY (Biotechnology)
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IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? Yes

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Product Quality Reviewer(s) Date

Branch Chief/Team Leader/Supervisor Date

Division Director Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MICHELE K DOUGHERTY
09/30/2013

SARAH B KENNETT
09/30/2013

KATHLEEN A CLOUSE STREBEL
09/30/2013